In Claim 6, the formulation is a beadlet which includes a core containing about 80 to about 100% by weight 2′,3′-dideoxyinosine.

Applicants are able to achieve the high concentration of 2',3'-dideoxyinosine in the composition claimed through use of a special process which is described on page 12 of the specification and in the working examples. As indicated on page 12, by dividing a dry blend of 2′,3′-dideoxyinosine, binder and disintegrant into two portions, one portion of which is made into beadlets using a spheronizer, and the other portion of which is dusted onto the beadlets during spheronization, Applicants are able to make their beadlets having the desired high concentration of 2′,3′-dideoxyinosine.

There is no disclosure or suggestion in any of the cited references of forming beadlets containing at least 80% by weight 2′,3′-dideoxyinosine or at least 80% by weight 2′,3′-dideoxyinosine in the core. This is not easily accomplished and it is through use of a unique 2′,3′-dideoxyinosine dusting step that such high concentrations are achievable.

It is submitted that Applicants' high potency 2′,3′-dideoxyinosine beadlets as claimed is patentable over all of the cited references each taken singly or in combination.

Claims 1, 4-24, 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morella et al. WO 94/03160, in view of Howard et al. US 5,049,394, and Bogardus et al. US 6,207,650. The Examiner contends that:

> "Morella teaches pelletized composition comprising core including 0.1 to 95% active ingredient, 0.1 to 55% binding agent, filler, carrier, excipients, and glidants (see abstract, and pages 6-7). The active ingredient can be erythromycin (page 4). The core is further being coated with 3 to 50% polymer, 0 to 50% plasticizer (pages 8-9, and formulations 1-7).
>
> "Howard teaches high drug load pharmaceutical composition comprising from about 80% to about 96% of drug, *e.g.,* erythromycin; from about 1 % to about 12% binder-plasticizer, such as, hydrophilic polymers; 0.5% to about 12% of starch-based excipient, such as, sodium starch glycolate, pregelatinized starch, or polyvinylpyrrolidone; and from about 0.2 to about 5% water-soluble binder, *e.g.,* hydroxypropylmethyl cellulose (columns 2-4). The composition is in spheronizer to form beads that may be coated with film former and plasticizer, and the coated beads can be filled into hard shell capsules (columns 4-5).
>
> "Howard and Morella are silent as to the teaching of 2',3'-dideoxyinosine as active agent.
>
> "Bogardus teaches pharmaceutical composition comprising antiviral drug, *e.g.,* 2',3'-dideoxyinosine in the form of powders, granules that can be enteric coated (columns 4-5). Accordingly, it would have been prima facie obvious for one of ordinary skill in the art to prepare the composition of Morella and Howard using 2',3'-dideoxyinosine as active ingredient in view of the teaching of Bogardus because the references teach the advantageous result of acid labile drug in oral dosage form."

Morella et al. discloses a pelletized sustained release pharmaceutical composition which includes a core element which includes 0.1 to 95% by weight of an active ingredient which as disclosed at pages 3 and 4 includes a

> "...xanthine oxidase inhibitor, antiarrhythmic, anticoagulant, gold compound, dopamine agonist, diuretic, anticancer, skeletal muscle relaxant, antimalarial, hormone, antipsychotic, antihistamine, immunosuppressive, antileprosy, carbonic anhydrase inhibitor, antibiotic, antifungal, corticosteroid, MAO-1, vasodilator, thyroid agent, sympatholytic, H_2-antagonist, stimulant, anticoagulant, anticonvulsant, antituberculosis, hypoglycaemic, glucocorticoid or antidepressant agent.
>
> "The active ingredient of low aqueous solubility may be an NSAID or an acid or salt thereof. The NSAID ingredient in the pelletized sustained release pharmaceutical composition according to the present invention may be selected from low aqueous solubility forms of Diclofenac, Etodolac, Fenoprofen, Fluorbiprofen, Ibuprofen, Ibuproxan, Indomethacin, Ketoprofen, Ketorolac, Nabumetone, Naproxen, Phenylbutazone, Piroxicam, Priprofen, Tolmetin, Aspirin, Sulinac, Diflunisal, Indoprofen, Mefanamic Acid, Fenclozic Acid, Alclofenac, Bucloxic Acid, Meclofenamic Acid, Flufenamic Acid, Cinchophen Cinmetacin, Ibufenac, Furobufen, Prodolic Acid, Oxoproxin, Clonixin, Fluprofen, Flutiazin. The present invention is particularly applicable to NSAID's of low aqueous solubility. Diclofenac, Ketorolac and Indomethacin are preferred.
>
> "The active ingredient of low aqueous solubility may be any other suitable ingredient, for example low aqueous solubility forms of Allopurinal, Amiodarone Hydrochloride, Anisindione, Auranofin, Benzocaine, Bromocriptine Mesylate, Bumetanide, Busulfan, Chlorambucil, Chloroquine, Chlorphenesin Carbomate, Chloprothixene, Clemastine Fumarate, Dehydrocholic Acid, Dichlorphenamide, Doxycycline Monohydrate, Erythromycin, Etoposide, Griseofulvin, Haloperidol, Hydrocortisone, Levothyroxine Sodium, Liothyronine Sodium, Lovastafin, Mephenytoin, Methazolamide, Methclothiazide, Metyrosine, Nitrofarantoin, Norfloxacin, Oestropipate, Famotadine, Pemoline, Phenacemide, Pimozide, Quinethazone, Rifampin, Sulfisoxazole, Tamoxifen Citrate, Tetracycline, Tolazamide, Triamcinolone, Trichlormethiaside, Trimethoprim, Trimipramine Maleate, Uracil Mustard and acids or salts thereof."

There is no disclosure or suggestion in Morella et al. of using 2′,3′-dideoxyinosine in their pellets. Accordingly, it is clear that Applicants' compositions as now claimed, which define the acid labile medicament as 2′,3′-dideoxyinosine, are neither anticipated nor made obvious by Morella et al. There is no disclosure or suggestion in Morella of a technique which would be applicable in making high concentration 2′,3′-dideoxyinosine beadlets as claimed herein. Thus, one skilled in the art reading Morella et al. could not make Applicants' beadlets employing the required drug dusting step since no drug dusting step is disclosed or suggested. Accordingly, since Morella et al. does not teach a way of making Applicants' beadlets, it is clear that Applicants' beadlets are patentable over Morella et al.

It is submitted that Applicants' invention as now claimed is patentable over Howard et al. As indicated, Applicants' composition as now claimed defines the acid labile medicament as 2′,3′-dideoxyinosine.

Howard et al. discloses beads containing more than about 80% by weight drug which drug may be an angiotensin converting enzyme (ACE) inhibitor, as well as

> "...anti-hypertensive agents such as nifedipine and verapamil, diuretics such as hydrochlorothiazide, bendroflumethiazide or chlorthalidone, beta-blockers such as propano-lol HCl or atenolol and anti-infectives such as erythromycin, beta lactams, penicillins, other macrolides or lincosamides." (Col. 3, lines 23 to 28)

As indicated above, Applicants' claims now define the acid labile medicament as 2′,3′-dideoxyinosine. There is no disclosure or suggestion in Howard et al. of a pharmaceutical composition which includes 2′,3′-dideoxyinosine as the pharmaceutical. There is no disclosure or suggestion in Howard et al. that the Howard et al. composition could be employed to carry 2′,3′-dideoxyinosine. Furthermore, there is no disclosure or suggestion in Howard et al. of how to make beadlets containing 2′,3′-dideoxyinosine containing high concentrations of drug. There is no disclosure or suggestion of a drug dusting step in Howard et al. which is necessary to prepare Applicants' beadlets. Accordingly, it is clear that Howard et al. does not anticipate or make obvious Applicants' composition as claimed.

As previously indicated, Morella et al. and Howard et al. disclose formulations which may be employed for various drugs none of which includes 2′,3′-dideoxyinosine. These references do not disclose or suggest Applicants' inventive concept of a composition containing at least 80% by weight 2′,3′-dideoxyinosine or a procedure for making a composition containing such a high concentration of 2′,3′-dideoxyinosine.

Accordingly, it is submitted that Applicants' invention as claimed is patentable over each of Morella et al. and Howard et al.

U.S. Patent No. 6,207,650 to Bogardus et al. discloses salts of 2′,3′-dideoxyinosine and pharmaceutical compositions containing salts of 2′,3′-dideoxyinosine which include tablets, lozenges, capsules, powders, and granules, but not BEADLETS or PELLETS, which may contain from about 0.5 to 100% by weight of a salt of 2′,3′-dideoxyinosine. There is no disclosure or suggestion of a beadlet or pellet containing at least 80% by weight 2′,3′-dideoxyinosine which is the base compound and not a salt thereof. This is Applicants' inventive concept and it is neither disclosed nor suggested in Bogardus et al. Bogardus et al. has nothing to do whatsoever with pellets or beadlets or how to make pellets or beadlets containing large amounts of 2′,3′-

dideoxyinosine and not a salt thereof. Accordingly, it is clear that Applicants' invention as claimed is patentable over Bogardus et al.

It is also submitted that Applicants' invention as claimed is patentable over a combination of Morella et al., taken in view of Howard et al. and Bogardus et al. Morella et al. and Howard et al. disclose hundreds, if not thousands, of possible drugs, none of which includes 2′,3′-dideoxyinosine. Furthermore, Morella et al. and Howard et al. do not disclose or suggest a procedure for making beadlets or pellets containing at least 80% by weight of the core of 2′,3′-dideoxyinosine which includes the required drug dusting step. Bogardus et al. disclose formulations containing salts of 2′,3′-dideoxyinosine but does not disclose or suggest beadlets or pellets, or beadlets or pellets containing at least 80% by weight 2′,3′-dideoxyinosine (and not a salt thereof). There is nothing in the teachings of Morella et al. and Howard et al. which would suggest to one skilled in the art that the Morella et al. and Howard et al. formulations could include 2′,3′-dideoxyinosine. All drug compounding techniques do not apply to all drugs. Bogardus et al. do not give the slightest hint or suggestion as to how to compound 2′,3′-dideoxyinosine into a formulation containing at least 80% by weight 2′,3′-dideoxyinosine in the core or otherwise. Bogardus et al. do not disclose or suggest a drug dusting step to make beadlets or pellets of high drug concentration as claimed herein. There is nothing in any of the cited references which suggests or gives the slightest hint that 2′,3′-dideoxyinosine could be compounded into a beadlet or pellet formulation containing at least 80% by weight 2′,3′-dideoxyinosine (and not a salt thereof). Even if the techniques of the cited references were combined, the combination would not disclose or suggest to one skilled in the art how a beadlet containing at least 80% 2′,3′-dideoxyinosine would be made. Accordingly, it is submitted that the cited combination of references are no more relevant than each taken alone and do not make Applicants' composition as claimed obvious.

Applicants are not claiming a process or a product by process herein. However, the fact that the cited references do not disclose or suggest a procedure for preparing beadlets or pellets of high concentration of 2′,3′-dideoxyinosine as claimed support Applicants' case for patentability of their beadlet containing at least 80% by weight 2′,3′-dideoxyinosine.

In view of the foregoing, it is believed that Claims 1, 4 to 24 and 27 to 31 are in condition for allowance.

Respectfully submitted,

Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
Princeton, NJ 08543-4000
(609) 252-4336

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Burton Rodney
Attorney for Applicants
Reg. No. 22,076